5495

CMA

CHEMICAL MANUFACTURERS ASSOCIATION

8EHQ-0498-14159

COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR

April 8, 1998

VIA CERTIFIED MAIL

Contains No CBI

Document Processing Center
Mail Code 7407
Room E-G99 East Tower
Office of Pollution Prevention and Toxics
Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

8EHQ-98-14159

Attention: TSCA § 8(e) Coordinator

88980000126

Dear Sir:

The Vinyl Chloride Health Committee of the Chemical Manufacturers Association submits the enclosed preliminary results from an ongoing inhalation two-generation reproductive toxicity study in Charles River CD rats sponsored by the Health Committee. These results are submitted pursuant to § 8(e) of the Toxic Substances Control Act.

As indicated in the enclosed preliminary macroscopic and microscopic pathology report, microscopic changes were seen in the livers of high-dose (1,100 parts per million (ppm)) parental rats of both generations. Hepatocellular hypertrophy was seen in the liver of all high-dose rats, and foci of cellular alteration in hepatocytes were significantly increased in the livers of P2 generation parental rats. An increased incidence of hepatocellular foci was seen in 18 of 30 high-dose males and 19 of 30 high-dose females. One focus of cellular alteration was seen in male controls; none was observed in females.

These effects are largely corroborative of results previously reported. Til, H.P. *et al.* observed a variety of treatment-related liver lesions in the high-dose (1.3 mg/kg body weight/day) group of Wistar rats tested in a lifetime oral carcinogenicity study of vinyl chloride. *Food Chem. Toxicol.* 29: 713-18 (1991). The lesions included increased incidences of liver cell polymorphism, hepatic cysts, foci of cellular alteration, neoplastic nodules, hepatocellular carcinomas, and angiosarcomas.

An earlier study of the age-dependence of the induction of pre-neoplastic enzyme-altered hepatic foci demonstrated that there is a period of increased sensitivity to the production of liver foci in response to vinyl chloride exposure in newborn rats. Lai R.L. *et al.*, *Carcinogenesis* 6: 65-68 (1985). This is consistent with the observation of hepatic foci induction in the P2, but not the P1, rats in the reproductive toxicity study. The P2 rats would presumably have been exposed to vinyl chloride during the lactation period (days 4-25 after birth), whereas the P1 animals would not. The period of sensitivity appears to correspond with the period of rapid increase in the number of cells of the liver (proliferation) in newborn rats.

Any significant supplemental data obtained as a result of further pathology evaluation will be reported in a follow-up communication.

The member companies of the CMA Vinyl Chloride Health Committee on whose behalf this submission is being made include:

Borden Chemicals and Plastics
180 E. Broad Street, 15th Fl.
Columbus, OH 43215
Panel Contact: Mr. Mark Gruenwald
Telephone: (614) 225-3459

CONDEA Vista Company
900 Threadneedle
P.O. Box 19029
Houston, TX 77079
Panel Contact: Dr. David A. Penney
Telephone: (281) 588-3059

The Dow Chemical Company
1803 Dow Center
Midland, MI 48674
Panel Contact: Dr. Colin Park
Telephone: (517) 636-1159

Formosa Plastics
9 Peachtree Hill Rd.
Livingston, NJ 07039
Panel Contact: Mr. David Pun
Telephone: (973) 716-7279

GEON Company
One Geon Center
Avon Lake, OH 44012
Panel Contact: Mr. Ed Beeler
Telephone: (440) 930-3030

Georgia Gulf Corporation
26100 Highway 405
P.O. Box 629
Plaquemine, LA 10165
Panel Contact: Mr. Jay Strange
Telephone: (504) 685-2642

Occidental Chemical Corp.
P.O. Box 809050
5005 LBJ Freeway, Room 904
Dallas, TX 75380
Panel Contact: Dr. Steve Phillips
Telephone: (972) 404-2413

PPG Industries, Inc.
One PPG Place - 36W
Pittsburgh, PA 15272
Panel Contact: Dr. James Barter
Telephone: (412) 434-2801

Westlake Chemical Corp.
2801 Post Oak Blvd.
Suite 600
Houston, TX 77056
Panel Contact: Mr. John Gamble
Telephone: (713) 960-9111

If you have any questions regarding this letter, please contact Wendy Sherman of my staff at (703) 741-5639.

Sincerely yours,

Courtney M. Price
Vice President, CHEMSTAR

Enclosure

cc: Vinyl Chloride Health Committee

Huntingdon

Ms Wendy Sherman
Chemical Manufacturers Association
Chemstar Department
1300 Wilson Boulevard
Arlington, VA 22209

20 March 1998

RE: Huntingdon Life Sciences Study No. 98-4080; Vinyl Chloride Combined Inhalation Two-Generation Reproduction and Developmental Toxicity Study in CD Rats: Preliminary Macroscopic and Microscopic Pathology Report and Organ Weight Data P1 and P2 parental animals.

Dear Wendy,

Attached for review are the following summary data for the referenced study.

1) Preliminary Macroscopic and Microscopic Pathology Report (2 pages);
2) Appendix M, Terminal Organ and Body Weights, Organ/Body Weight and Organ/Brain Weight Ratios - P1 and P2 Parental Generations (22 pages).

These organ weight data (Appendix M) have not been audited by our Quality Assurance Unit but they have been reviewed and I would not expect these values to change significantly following an audit. If you have any comments or questions concerning the enclosed or if you require additional information, please let me know.

Best Regards

Ray

Raymond E. Schroeder, M.S., D.A.B.T.
Study Director

Enclosures
cc: Dr. Dave Penny

96-4080: VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

Preliminary Macroscopic and Microscopic Pathology Report

1. INTRODUCTION

This study was conducted as a combined inhalation two-generation reproduction and developmental toxicity study in rats with vinyl chloride. The purposes of this study were to evaluate effects of the test material on parental toxicity, reproductive capacity, in utero development, and neonatal growth and survival in rats.

A limited microscopic pathology evaluation (Protocol Appendix A - approximately 15-18 tissues/animal) was performed on all P1 and P2 animals in the control and high-dose group (1100 ppm). Additionally, a detailed examination of the turbinates and upper respiratory tract (four levels) was performed on all animals scheduled for microscopic evaluation.

2. GROSS PATHOLOGY

None of the macroscopic observations in the P1 and P2 parental animals were judged related to treatment with the test material. Incidental or spontaneous findings occurred sporadically in rats from the control and treated groups and have been seen in Charles River CD rats of similar age used in other studies conducted in this facility.

3. MICROSCOPIC PATHOLOGY

Microscopic test article-related changes were seen in the livers of high-dose parental rats of both generations. Hepatocellular hypertrophy was seen in the liver of all high dose rats; also foci of cellular alteration in hepatocytes were greatly increased in the livers of P2 generation parental rats.

An increased incidence of foci of cellular alteration in hepatocytes was seen in the high-dose P2 parental rats only. These lesions were coded as "acidophilic focus", "basophilic focus", or "clear cell focus" and were considered together for purposes of evaluation. Lesion classification was based primarily on the tinctorial properties of the affected cells. Affected cells may be smaller or larger than normal and are distinct from surrounding hepatocytes based on the staining characteristics with H&E stains. A few of these lesions contained rare mitotic figures and there was a clear demarcation from the surrounding tissue. There was a general absence of cellular atypia in these lesions. The foci identified in these animals were usually solitary in occurrence i.e. Only one focus was identified in the liver for each rat examined. However, a few rats had several foci of cellular alteration present in the two sections of liver tissue examined. These hepatic foci are considered to be proliferative in nature and may be considered an adverse finding depending on the type of study in which they are seen.

Generally, increased incidences of hepatocellular alteration are seen in aged, untreated rats of this strain fed ad libitum. However, an incidence exceeding 50% in young animals as seen in this study, is clearly indicative of a test-article-related effect.

The following histomorphologic criteria were used in classifying the foci of cellular alteration:

Acidophilic Focus- cells moderately to greatly enlarged with increased amounts of cytoplasm; cytoplasm pale and eosinophilic.

Basophilic Focus- cells usually enlarged to a slight or moderate degree; cytoplasm stains diffusely and homogeneously basophilic.

Clear Cell Focus- cells may be slightly to greatly enlarged; cytoplasm appears empty and unstained[1].

The incidences of hepatocellular foci and hepatocellular hypertrophy are presented in the following table:

Selected Microscopic Findings in the Liver								
Generation	**P1**				**P2**			
Sex	**Males**		**Females**		**Males**		**Females**	
Group	**I**	**IV**	**I**	**IV**	**I**	**IV**	**I**	**IV**
Number of Animals Examined	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**
Acidophilic Focus	0	1	0	0	1	5	0	8
Basophilic Focus	0	1	0	0	0	8	0	11
Clear Cell Focus	0	0	0	0	0	5	0	0
Total	**0**	**2**	**0**	**0**	**1**	**18**	**0**	**19**
Hepatocellular Hypertrophy (Centrilobular)	0	30	0	30	0	30	0	30

Hepatocellular hypertrophy was seen in the livers of all treated rats in both generations. The hepatocytes were enlarged with increased acidophilic cytoplasm in the centrilobular areas of the lobule. This observation correlates with the increased liver weights seen in the high-dose animals in this experiment and is generally considered to represent an adaptive change by the hepatocytes.

Other findings occurred with comparable incidence or severity or they occurred sporadically in rats from the control and high-dose groups. These incidental findings were not considered to be related to the test material and have been seen in rats of similar age and strain used in other studies conducted in this facility.

---

[1] Proliferative and selected other Lesions in the Liver of Rats. STP Guides for Toxicologic Pathology, Washington, DC STP/AFIP 1994.

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P1 GENERATION - MALES

MEAN VALUES

	TERMINAL BODY WT. (G)	BRAIN WT. (G)	BRAIN ORG/TBW (X 1000)	BRAIN ORG/BRN (X 1)	ADRENALS WT. (G)	ADRENALS ORG/TBW (X 10000)	ADRENALS ORG/BRN (X 100)
GROUP I - 0 PPM							
MEAN	504.9	2.251	4.48	1.00	.0684	1.36	3.04
S.D.	40.2	.113	.40	.00	.0120	.24	.52
N	15	15	15	15	15	15	15
GROUP II - 10 PPM							
MEAN	530.7	2.223	4.22	1.00	.0707	1.34	3.18
S.D.	46.3	.066	.36	.00	.0106	.20	.47
N	15	15	15	15	15	15	15
GROUP III - 100 PPM							
MEAN	524.0	2.256	4.31	1.00	.0704	1.34	3.13
S.D.	22.9	.108	.22	.00	.0143	.26	.66
N	15	15	15	15	15	15	15
GROUP IV - 1100 PPM							
MEAN	514.8	2.229	4.34	1.00	.0704	1.37	3.16
S.D.	35.7	.097	.23	.00	.0102	.17	.45
N	15	15	15	15	15	15	15

No statistically significant differences from control mean.

DRAFT

96-4080

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P1 GENERATION - MALES

MEAN VALUES

	TERMINAL BODY WT. (G)	KIDNEYS WT. (G)	KIDNEYS ORG/TBW (X 1000)	KIDNEYS ORG/BRN (X 1)	LIVER WT. (G)	LIVER ORG/TBW (X 100)	LIVER ORG/BRN (X 1)
GROUP I - 0 PPM							
MEAN	504.9	4.148	8.24	1.85	14.324	2.83	6.38
S.D.	40.2	.304	.64	.17	2.134	.26	1.07
N	15	15	15	15	15	15	15
GROUP II - 10 PPM							
MEAN	530.7	4.301	8.12	1.94	16.201*	3.05*	7.30
S.D.	46.3	.456	.73	.21	2.193	.29	1.02
N	15	15	15	15	15	15	15
GROUP III - 100 PPM							
MEAN	524.0	4.468	8.53	1.99	16.216*	3.09*	7.20*
S.D.	22.9	.285	.54	.17	1.586	.20	.74
N	15	15	15	15	15	15	15
GROUP IV - 1100 PPM							
MEAN	514.8	4.311	8.39	1.93	16.718**	3.26**	7.51**
S.D.	35.7	.303	.51	.10	.857	.19	.38
N	15	15	15	15	15	15	15

*,**Statistically different from control mean; $p \leq 0.05$, $p \leq 0.01$.

DRAFT

96-4080

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P1 GENERATION - MALES

	MEAN VALUES						
	TERMINAL BODY WT. (G)	LUNGS WT. (G)	LUNGS ORG/TBW (X 1000)	LUNGS ORG/BRN (X 10)	PROSTATE WT. (G)	PROSTATE ORG/TBW (X 1000)	PROSTATE ORG/BRN (X 10)
GROUP I - 0 PPM							
MEAN	504.9	1.828	3.62	8.12	.899	1.78	3.99
S.D.	40.2	.183	.28	.77	.173	.34	.78
N	15	15	15	15	15	15	15
GROUP II - 10 PPM							
MEAN	530.7	1.883	3.55	8.46	1.005	1.90	4.51
S.D.	46.3	.208	.30	.81	.259	.48	1.12
N	15	15	15	15	15	15	15
GROUP III - 100 PPM							
MEAN	524.0	1.884	3.60	8.37	1.051	2.01	4.66
S.D.	22.9	.122	.25	.69	.278	.52	1.22
N	15	15	15	15	15	15	15
GROUP IV - 1100 PPM							
MEAN	514.8	1.924	3.75	8.65	1.011	1.96	4.54
S.D.	35.7	.159	.28	.82	.264	.48	1.20
N	15	15	15	15	15	15	15

No statistically significant differences from control mean.

DRAFT

96-4080

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P1 GENERATION - MALES

		MEAN VALUES					
	TERMINAL	SEMIN VESI			SPLEEN		
	BODY WT. (G)	WT. (G)	ORG/TBW (X 1000)	ORG/BRN (X 1)	WT. (G)	ORG/TBW (X 1000)	ORG/BRN (X 10)
GROUP I - 0 PPM							
MEAN	504.9	2.3527	4.72	1.05	.824	1.63	3.67
S.D.	40.2	.5185	1.24	.24	.113	.18	.56
N	15	15	15	15	15	15	15
GROUP II - 10 PPM							
MEAN	530.7	2.2269	4.24	1.00	.804	1.52	3.62
S.D.	46.3	.4496	.96	.20	.102	.14	.42
N	15	15	15	15	15	15	15
GROUP III - 100 PPM							
MEAN	524.0	2.3967	4.60	1.06	.863	1.65	3.83
S.D.	22.9	.4629	.97	.21	.100	.18	.42
N	15	15	15	15	15	15	15
GROUP IV - 1100 PPM							
MEAN	514.8	2.3444	4.55	1.05	.892	1.73	4.00
S.D.	35.7	.4376	.78	.19	.140	.22	.56
N	15	15	15	15	15	15	15

No statistically significant differences from control mean.

DRAFT

96-4080

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P1 GENERATION - MALES

MEAN VALUES

	TERMINAL BODY WT. (G)	R. EPIDIDYMID WT. (G)	R. EPIDIDYMID ORG/TBW (X 1000)	R. EPIDIDYMID ORG/BRN (X 10)	TESTES WT. (G)	TESTES ORG/TBW (X 1000)	TESTES ORG/BRN (X 1)
GROUP I - 0 PPM							
MEAN	504.9	.7034	1.40	3.13	3.461	6.88	1.54
S.D.	40.2	.0571	.16	.23	.241	.59	.14
N	15	15	15	15	15	15	15
GROUP II - 10 PPM							
MEAN	530.7	.7564	1.44	3.40	3.535	6.72	1.59
S.D.	46.3	.0998	.23	.44	.489	1.23	.22
N	15	15	15	15	15	15	15
GROUP III - 100 PPM							
MEAN	524.0	.7791	1.49	3.46*	3.617	6.92	1.61
S.D.	22.9	.0704	.14	.32	.201	.57	.13
N	15	15	15	15	15	15	15
GROUP IV - 1100 PPM							
MEAN	514.8	.7596	1.48	3.41	3.479	6.80	1.56
S.D.	35.7	.0801	.15	.38	.386	.90	.18
N	15	15	15	15	15	15	15

*Statistically different from control mean; $p \leq 0.05$.

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P1 GENERATION - MALES

	MEAN VALUES			
	TERMINAL BODY WT. (G)	THYMUS WT. (G)	THYMUS ORG/TBW (X 10000)	THYMUS ORG/BRN (X 10)
GROUP I - 0 PPM				
MEAN	504.9	.265	5.22	1.17
S.D.	40.2	.068	1.13	.28
N	15	15	15	15
GROUP II - 10 PPM				
MEAN	530.7	.276	5.19	1.24
S.D.	46.3	.073	1.29	.33
N	15	15	15	15
GROUP III - 100 PPM				
MEAN	524.0	.292	5.57	1.30
S.D.	22.9	.072	1.36	.35
N	15	15	15	15
GROUP IV - 1100 PPM				
MEAN	514.8	.294	5.76	1.33
S.D.	35.7	.047	1.12	.24
N	15	15	15	15

No statistically significant differences from control mean.

DRAFT

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P1 GENERATION - FEMALES

MEAN VALUES

	TERMINAL BODY WT. (G)	BRAIN WT. (G)	BRAIN ORG/TBW (X 1000)	BRAIN ORG/BRN (X 1)	ADRENALS WT. (G)	ADRENALS ORG/TBW (X 10000)	ADRENALS ORG/BRN (X 100)
GROUP I - 0 PPM							
MEAN	291.6	2.103	7.22	1.00	.0701	2.41	3.34
S.D.	12.4	.103	.39	.00	.0086	.33	.46
N	15	15	15	15	15	15	15
GROUP II - 10 PPM							
MEAN	286.8	2.074	7.25	1.00	.0755	2.64	3.64
S.D.	17.7	.079	.43	.00	.0095	.35	.45
N	15	15	15	15	15	15	15
GROUP III - 100 PPM							
MEAN	288.5	2.028	7.05	1.00	.0738	2.57	3.64
S.D.	19.6	.057	.42	.00	.0103	.43	.53
N	15	15	15	15	15	15	15
GROUP IV - 1100 PPM							
MEAN	281.8	2.069	7.35	1.00	.0689	2.47	3.34
S.D.	17.8	.101	.57	.00	.0094	.36	.48
N	14	15	14	15	15	14	15

No statistically significant differences from control mean.

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P1 GENERATION - FEMALES

MEAN VALUES

	TERMINAL BODY WT. (G)	KIDNEYS WT. (G)	KIDNEYS ORG/TBW (X 1000)	KIDNEYS ORG/BRN (X 1)	LIVER WT. (G)	LIVER ORG/TBW (X 100)	LIVER ORG/BRN (X 1)
GROUP I - 0 PPM							
MEAN	291.6	2.542	8.71	1.21	9.625	3.31	4.58
S.D.	12.4	.277	.79	.12	.876	.32	.42
N	15	15	15	15	15	15	15
GROUP II - 10 PPM							
MEAN	286.8	2.507	8.76	1.21	9.542	3.34	4.61
S.D.	17.7	.247	.91	.13	.966	.36	.50
N	15	15	15	15	15	15	15
GROUP III - 100 PPM							
MEAN	288.5	2.585	8.97	1.28	9.800	3.40	4.83
S.D.	19.6	.269	.84	.14	1.103	.30	.48
N	15	15	15	15	15	15	15
GROUP IV - 1100 PPM							
MEAN	281.8	2.588	9.10	1.25	10.028	3.55	4.87
S.D.	17.8	.253	.70	.13	.967	.31	.60
N	14	15	14	15	15	14	15

No statistically significant differences from control mean.

DRAFT

96-4080

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P1 GENERATION - FEMALES

		MEAN VALUES					
	TERMINAL	LUNGS			OVARIES		
	BODY WT. (G)	WT. (G)	ORG/TBW (X 1000)	ORG/BRN (X 10)	WT. (G)	ORG/TBW (X 10000)	ORG/BRN (X 100)
GROUP I - 0 PPM							
MEAN	291.6	1.426	4.90	6.82	.1042	3.57	4.97
S.D.	12.4	.107	.30	.66	.0145	.48	.74
N	15	14	14	14	15	15	15
GROUP II - 10 PPM							
MEAN	286.8	1.451	5.07	7.01	.1081	3.78	5.23
S.D.	17.7	.144	.56	.75	.0244	.88	1.29
N	15	15	15	15	15	15	15
GROUP III - 100 PPM							
MEAN	288.5	1.402	4.87	6.92	.1025	3.55	5.06
S.D.	19.6	.093	.24	.45	.0194	.57	.95
N	15	15	15	15	15	15	15
GROUP IV - 1100 PPM							
MEAN	281.8	1.434	5.09	6.95	.1091	3.88	5.28
S.D.	17.8	.157	.41	.85	.0166	.58	.78
N	14	15	14	15	15	14	15

No statistically significant differences from control mean.

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P1 GENERATION - FEMALES

MEAN VALUES

	TERMINAL BODY WT. (G)	SPLEEN WT. (G)	SPLEEN ORG/TBW (X 1000)	SPLEEN ORG/BRN (X 10)	THYMUS WT. (G)	THYMUS ORG/TBW (X 10000)	THYMUS ORG/BRN (X 10)
GROUP I - 0 PPM							
MEAN	291.6	.569	1.95	2.71	.234	8.05	1.11
S.D.	12.4	.095	.26	.48	.063	2.19	.30
N	15	15	15	15	15	15	15
GROUP II - 10 PPM							
MEAN	286.8	.713**	2.50**	3.45**	.236	8.21	1.14
S.D.	17.7	.118	.46	.61	.055	1.72	.26
N	15	15	15	15	15	15	15
GROUP III - 100 PPM							
MEAN	288.5	.633	2.19	3.13	.291	10.18	1.44
S.D.	19.6	.187	.57	.93	.121	4.65	.61
N	15	15	15	15	15	15	15
GROUP IV - 1100 PPM							
MEAN	281.8	.598	2.15	2.89	.233	8.31	1.13
S.D.	17.8	.063	.22	.31	.060	2.11	.30
N	14	15	14	15	15	14	15

**Statistically different from control mean; $p \leq 0.01$.

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P1 GENERATION - FEMALES

	MEAN VALUES			
	TERMINAL BODY WT. (G)	UTERUS WT. (G)	UTERUS ORG/TBW (X 1000)	UTERUS ORG/BRN (X 10)
GROUP I - 0 PPM				
MEAN	291.6	.644	2.20	3.06
S.D.	12.4	.179	.57	.84
N	15	15	15	15
GROUP II - 10 PPM				
MEAN	286.8	.692	2.43	3.35
S.D.	17.7	.118	.47	.61
N	15	15	15	15
GROUP III - 100 PPM				
MEAN	288.5	.667	2.31	3.29
S.D.	19.6	.155	.47	.74
N	15	15	15	15
GROUP IV - 1100 PPM				
MEAN	281.8	.637	2.23	3.09
S.D.	17.8	.095	.31	.49
N	14	15	14	15

No statistically significant differences from control mean.

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P2 GENERATION - MALES

MEAN VALUES

	TERMINAL BODY WT. (G)	BRAIN WT. (G)	BRAIN ORG/TBW (X 1000)	BRAIN ORG/BRN (X 1)	ADRENALS WT. (G)	ADRENALS ORG/TBW (X 10000)	ADRENALS ORG/BRN (X 100)
GROUP I - 0 PPM							
MEAN	472.4	2.156	4.59	1.00	.0637	1.36	2.97
S.D.	46.3	.119	.40	.00	.0161	.35	.77
N	15	15	15	15	15	15	15
GROUP II - 10 PPM							
MEAN	499.0	2.241	4.56	1.00	.0664	1.31	2.94
S.D.	71.3	.107	.50	.00	.0163	.29	.68
N	15	15	15	15	14	14	14
GROUP III - 100 PPM							
MEAN	500.0	2.208	4.44	1.00	.0633	1.27	2.86
S.D.	39.5	.084	.33	.00	.0094	.19	.40
N	15	15	15	15	15	15	15
GROUP IV - 1100 PPM							
MEAN	503.6	2.203	4.39	1.00	.0684	1.37	3.13
S.D.	31.8	.124	.35	.00	.0119	.24	.60
N	15	15	15	15	14	14	14

No statistically significant differences from control mean.

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P2 GENERATION - MALES

MEAN VALUES

	TERMINAL BODY WT. (G)	KIDNEYS WT. (G)	KIDNEYS ORG/TBW (X 1000)	KIDNEYS ORG/BRN (X 1)	LIVER WT. (G)	LIVER ORG/TBW (X 100)	LIVER ORG/BRN (X 1)
GROUP I - 0 PPM							
MEAN	472.4	3.912	8.29	1.81	14.133	2.98	6.55
S.D.	46.3	.444	.52	.18	2.363	.33	.99
N	15	15	15	15	15	15	15
GROUP II - 10 PPM							
MEAN	499.0	4.253	8.54	1.89	15.072	3.01	6.70
S.D.	71.3	.609	.65	.22	2.742	.19	1.03
N	15	15	15	15	15	15	15
GROUP III - 100 PPM							
					*	**	*
MEAN	500.0	4.249	8.51	1.93	16.619	3.32	7.54
S.D.	39.5	.453	.79	.22	2.265	.36	1.08
N	15	15	15	15	15	15	15
GROUP IV - 1100 PPM							
					**	**	**
MEAN	503.6	4.236	8.42	1.93	17.013	3.38	7.74
S.D.	31.8	.361	.64	.17	1.494	.19	.75
N	15	15	15	15	15	15	15

*,**Statistically different from control mean; $p \leq 0.05$, $p \leq 0.01$.

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P2 GENERATION - MALES

	MEAN VALUES						
	TERMINAL BODY WT. (G)	LUNGS WT. (G)	LUNGS ORG/TBW (X 1000)	LUNGS ORG/BRN (X 10)	PROSTATE WT. (G)	PROSTATE ORG/TBW (X 1000)	PROSTATE ORG/BRN (X 10)
GROUP I - 0 PPM							
MEAN	472.4	1.709	3.62	7.93	.806	1.71	3.75
S.D.	46.3	.215	.29	.85	.239	.50	1.17
N	15	15	15	15	15	15	15
GROUP II - 10 PPM							
MEAN	499.0	1.806	3.63	8.04	.858	1.74	3.83
S.D.	71.3	.258	.37	.93	.251	.46	1.08
N	15	15	15	15	14	14	14
GROUP III - 100 PPM							
MEAN	500.0	1.844	3.70	8.35	.856	1.72	3.89
S.D.	39.5	.200	.38	.86	.248	.51	1.20
N	15	15	15	15	15	15	15
GROUP IV - 1100 PPM							
MEAN	503.6	1.856	3.69	8.44	.892	1.77	4.08
S.D.	31.8	.233	.40	1.12	.225	.41	1.11
N	15	15	15	15	15	15	15

No statistically significant differences from control mean.

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P2 GENERATION - MALES

MEAN VALUES

	TERMINAL BODY WT. (G)	SEMIN VESI WT. (G)	SEMIN VESI ORG/TBW (X 1000)	SEMIN VESI ORG/BRN (X 1)	SPLEEN WT. (G)	SPLEEN ORG/TBW (X 1000)	SPLEEN ORG/BRN (X 10)
GROUP I - 0 PPM							
MEAN	472.4	2.3964	5.11	1.11	.761	1.61	3.53
S.D.	46.3	.3250	.82	.15	.140	.24	.60
N	15	15	15	15	15	15	15
GROUP II - 10 PPM							
MEAN	499.0	2.2789	4.57	1.01	.789	1.58	3.52
S.D.	71.3	.5992	1.13	.25	.204	.33	.88
N	15	15	15	15	15	15	15
GROUP III - 100 PPM							
MEAN	500.0	2.3378	4.70	1.06	.901	1.79	4.08
S.D.	39.5	.4271	.88	.21	.209	.31	.90
N	15	15	15	15	15	15	15
GROUP IV - 1100 PPM							
					*	*	*
MEAN	503.6	2.0940	4.14	.95	.987	1.96	4.48
S.D.	31.8	.5071	.90	.23	.246	.50	1.11
N	15	15	15	15	15	15	15

*Statistically different from control mean; $p \leq 0.05$.

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P2 GENERATION - MALES

MEAN VALUES

	TERMINAL BODY WT. (G)	R. EPIDIDYMID WT. (G)	R. EPIDIDYMID ORG/TBW (X 1000)	R. EPIDIDYMID ORG/BRN (X 10)	TESTES WT. (G)	TESTES ORG/TBW (X 1000)	TESTES ORG/BRN (X 1)
GROUP I - 0 PPM							
MEAN	472.4	.7071	1.50	3.30	3.282	6.98	1.53
S.D.	46.3	.1023	.21	.53	.529	1.17	.26
N	15	15	15	15	15	15	15
GROUP II - 10 PPM							
MEAN	499.0	.7362	1.50	3.28	3.413	6.93	1.52
S.D.	71.3	.0901	.26	.36	.272	.83	.11
N	15	15	15	15	15	15	15
GROUP III - 100 PPM							
MEAN	500.0	.7055	1.42	3.20	3.464	6.95	1.57
S.D.	39.5	.0619	.14	.30	.366	.78	.19
N	15	15	15	15	15	15	15
GROUP IV - 1100 PPM							
MEAN	503.6	.6862	1.37	3.13	3.299	6.57	1.50
S.D.	31.8	.1186	.25	.60	.540	1.15	.25
N	15	15	15	15	15	15	15

No statistically significant differences from control mean.

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P2 GENERATION - MALES

	MEAN VALUES			
	TERMINAL BODY WT. (G)	THYMUS WT. (G)	THYMUS ORG/TBW (X 10000)	THYMUS ORG/BRN (X 10)
GROUP I - 0 PPM				
MEAN	472.4	.247	5.28	1.15
S.D.	46.3	.045	1.08	.23
N	15	15	15	15
GROUP II - 10 PPM				
MEAN	499.0	.296	5.97	1.32
S.D.	71.3	.078	1.50	.33
N	15	15	15	15
GROUP III - 100 PPM				
MEAN	500.0	.268	5.36	1.21
S.D.	39.5	.062	1.22	.26
N	15	15	15	15
GROUP IV - 1100 PPM				
MEAN	503.6	.302	5.96	1.37
S.D.	31.8	.113	2.14	.54
N	15	15	15	15

No statistically significant differences from control mean.

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P2 GENERATION - FEMALES

	MEAN VALUES						
	TERMINAL BODY WT. (G)	BRAIN WT. (G)	BRAIN ORG/TBW (X 1000)	BRAIN ORG/BRN (X 1)	ADRENALS WT. (G)	ADRENALS ORG/TBW (X 10000)	ADRENALS ORG/BRN (X 100)
GROUP I - 0 PPM							
MEAN	274.1	2.067	7.66	1.00	.0716	2.65	3.47
S.D.	32.2	.106	1.19	.00	.0103	.52	.48
N	15	15	15	15	15	15	15
GROUP II - 10 PPM							
MEAN	283.9	2.061	7.27	1.00	.0719	2.54	3.51
S.D.	14.4	.119	.41	.00	.0122	.47	.66
N	15	15	15	15	15	15	15
GROUP III - 100 PPM							
MEAN	286.0	2.008	7.04	1.00	.0736	2.57	3.68
S.D.	25.2	.174	.52	.00	.0132	.38	.67
N	15	15	15	15	15	15	15
GROUP IV - 1100 PPM							
MEAN	279.7	2.010	7.23	1.00	.0736	2.64	3.66
S.D.	30.2	.144	.54	.00	.0082	.19	.36
N	15	15	15	15	15	15	15

No statistically significant differences from control mean.

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P2 GENERATION - FEMALES

MEAN VALUES

	TERMINAL BODY WT. (G)	KIDNEYS WT. (G)	KIDNEYS ORG/TBW (X 1000)	KIDNEYS ORG/BRN (X 1)	LIVER WT. (G)	LIVER ORG/TBW (X 100)	LIVER ORG/BRN (X 1)
GROUP I - 0 PPM							
MEAN	274.1	2.426	8.92	1.18	9.589	3.54	4.65
S.D.	32.2	.272	1.17	.14	1.433	.66	.71
N	15	15	15	15	15	15	15
GROUP II - 10 PPM							
MEAN	283.9	2.446	8.62	1.19	9.545	3.37	4.65
S.D.	14.4	.181	.62	.09	1.117	.42	.63
N	15	15	15	15	15	15	15
GROUP III - 100 PPM							
MEAN	286.0	2.528	8.86	1.26	10.249	3.60	5.13
S.D.	25.2	.246	.70	.09	1.285	.45	.64
N	15	15	15	15	15	15	15
GROUP IV - 1100 PPM							
MEAN	279.7	2.458	8.83	1.23	10.422	3.74	5.20
S.D.	30.2	.254	.74	.13	1.108	.38	.62
N	15	15	15	15	15	15	15

No statistically significant differences from control mean.

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P2 GENERATION - FEMALES

MEAN VALUES

	TERMINAL BODY WT. (G)	LUNGS WT. (G)	LUNGS ORG/TBW (X 1000)	LUNGS ORG/BRN (X 10)	OVARIES WT. (G)	OVARIES ORG/TBW (X 10000)	OVARIES ORG/BRN (X 100)
GROUP I - 0 PPM							
MEAN	274.1	1.310	4.87	6.28	.1077	3.98	5.22
S.D.	32.2	.117	.86	.43	.0226	.99	1.10
N	15	14	14	14	15	15	15
GROUP II - 10 PPM							
MEAN	283.9	1.369	4.82	6.65	.0967	3.40	4.67
S.D.	14.4	.113	.33	.55	.0216	.73	.86
N	15	15	15	15	15	15	15
GROUP III - 100 PPM							
MEAN	286.0	1.357	4.74	6.77	.1019	3.57	5.07
S.D.	25.2	.180	.38	.72	.0211	.73	.96
N	15	15	15	15	15	15	15
GROUP IV - 1100 PPM							
MEAN	279.7	1.367	4.93	6.82	.1009	3.62	5.02
S.D.	30.2	.118	.56	.60	.0268	.87	1.26
N	15	15	15	15	15	15	15

No statistically significant differences from control mean.

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P2 GENERATION - FEMALES

MEAN VALUES

	TERMINAL BODY WT. (G)	SPLEEN WT. (G)	SPLEEN ORG/TBW (X 1000)	SPLEEN ORG/BRN (X 10)	THYMUS WT. (G)	THYMUS ORG/TBW (X 10000)	THYMUS ORG/BRN (X 10)
GROUP I - 0 PPM							
MEAN	274.1	.579	2.14	2.80	.249	9.16	1.22
S.D.	32.2	.126	.53	.60	.086	3.14	.47
N	15	15	15	15	15	15	15
GROUP II - 10 PPM							
MEAN	283.9	.538	1.90	2.62	.217	7.67	1.06
S.D.	14.4	.072	.26	.42	.039	1.43	.19
N	15	15	15	15	15	15	15
GROUP III - 100 PPM							
MEAN	286.0	.571	1.99	2.85	.265	9.33	1.34
S.D.	25.2	.091	.25	.40	.051	1.91	.33
N	15	15	15	15	15	15	15
GROUP IV - 1100 PPM							
MEAN	279.7	.604	2.16	3.00	.235	8.43	1.16
S.D.	30.2	.076	.22	.30	.063	2.25	.28
N	15	15	15	15	15	15	15

No statistically significant differences from control mean.

APPENDIX M (CONT.)
VINYL CHLORIDE COMBINED INHALATION TWO-GENERATION
REPRODUCTION AND DEVELOPMENTAL TOXICITY STUDY IN CD RATS

TERMINAL ORGAN AND BODY WEIGHTS,
ORGAN/BODY WEIGHT AND ORGAN/BRAIN WEIGHT RATIOS
TERMINAL SACRIFICE - P2 GENERATION - FEMALES

	MEAN VALUES			
	TERMINAL BODY WT. (G)	UTERUS WT. (G)	UTERUS ORG/TBW (X 1000)	UTERUS ORG/BRN (X 10)
GROUP I - 0 PPM				
MEAN	274.1	.722	2.66	3.49
S.D.	32.2	.177	.68	.81
N	15	15	15	15
GROUP II - 10 PPM				
MEAN	283.9	.727	2.56	3.53
S.D.	14.4	.259	.92	1.27
N	15	15	15	15
GROUP III - 100 PPM				
MEAN	286.0	.706	2.51	3.56
S.D.	25.2	.164	.69	.93
N	15	15	15	15
GROUP IV - 1100 PPM				
MEAN	279.7	.687	2.47	3.41
S.D.	30.2	.175	.64	.79
N	15	15	15	15

No statistically significant differences from control mean.